FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **5661-01-DRK**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **10/019993**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/01788	**10 May 2000**	**10 May 1999**

TITLE OF INVENTION
AROMATIC AMIDES

APPLICANT(S) FOR DO/EO/US
BRYANS, Justin Stephen; O'TOOLE, John Colm; HORWELL, David Christopher

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

PCT application as published

Express Mail No. ET401306226US

531 Rec'd PCT/PTO 09 NOV 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/019995	PCT/GB00/01788	5661-01-DRK

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☒	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	$970.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	$840.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$690.00
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$670.00
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$96.00

ENTER APPROPRIATE BASIC FEE AMOUNT = $970.00

Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)). $0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	28 - 20 =	8	x $18.00	$144.00
Independent claims	9 - 3 =	6	x $84.00	$504.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00

TOTAL OF ABOVE CALCULATIONS = $1,618.00

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐ $0.00

SUBTOTAL = $1,618.00

Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). + $0.00

TOTAL NATIONAL FEE = $1,618.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐ $0.00

TOTAL FEES ENCLOSED = $1,618.00

Amount to be: refunded $

charged $

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **23-0455** in the amount of **$1,618.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **23-0455** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

David R. Kurlandsky
Registration No. 41,505

Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (734) 622-7304
Fax (734) 622-1553

SIGNATURE

David R. Kurlandsky
NAME

41,505
REGISTRATION NUMBER

09 November 2001
DATE

PD-5661-01-DRK

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT : JUSTIN STEPHEN BRYANS, ET AL. EXAMINER :

SERIAL NO : ART UNIT :

FILED : PAPER NO :

FOR : AROMATIC AMIDES

PRELIMINARY AMENDMENT

November 9, 2001

BOX PCT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is a Preliminary Amendment for a 371 filing of PCT/GB00/01788 filed May 10, 2000.

Please enter the following amendments and remarks in the present application.

IN THE SPECIFICATION:

On page 1 at line 3 after the title insert

-- CROSS REFERENCE TO RELATED APPLICATIONS

This application is a 371 filing of PCT/GB00/01788 filed May 10, 2000, priority based on Provisional Application No. 60/133,359 filed May 10, 1999. --

IN THE CLAIMS:

Cancel Claims 15, 24, 25 and 26.

Add the following new Claims 29-32.

Claim 29 (new). A compound according to Claim 5 which is selected from

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone;

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-bromonaphthalene;

N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-(3-diethylamino-propyl))-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-Diethylaminoethyl)-1-4-azidonaphthalene;

N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzyl-amine;

N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine;

N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene;

N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide;

N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene; and

N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

Claim 30 (new). A compound according to Claim 1 which is a pharmaceutically acceptable salt.

Claim 31 (new). A pharmaceutical formulation comprising a compound of Claim 1 together with a pharmaceutically acceptable diluent, carrier or excipient therefor.

Claim 32 (new). A method for treating a CNS disorder in a mammal in need of treatment comprising administering a CNS effective amount of a compound of Claim 1.

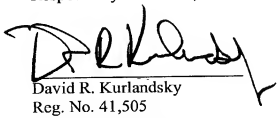
REMARKS

Claims 1-14, 16-23 and 27-32 are all the claims under consideration in the application. Claims 15, 24, 25 and 26 are cancelled. New Claims 29-32 are added.

A cross-reference to the parent application is added after the title. No new matter is added. New Claims 29-32 recite the subject matter of cancelled Claims 15, 24, 25 and 26, respectively.

Applicants request prosecution of this application on the merits.

Respectfully submitted,



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Attachment - Amended claims, Version with markings to show changes made

DK1P4439.doc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Cancel Claims 15, 24, 25 and 26.

Add the following new Claims 29-32.

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N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene;

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N-Propionyl, N-(2-Diethylaminoethyl)-1-4-azidonaphthalene;

N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzyl-amine;

N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine;

N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene;

N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene;

N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide;

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Claim 32 (new). A method for treating a CNS disorder in a mammal in need of treatment comprising administering a CNS effective amount of a compound of Claim 1.

AROMATIC AMIDES

FIELD OF THE INVENTION

This invention provides aromatic amides which are useful CNS agents, especially for treating depression, pain, anxiety, schizophrenia and seizure disorders.

BACKGROUND OF THE INVENTION

Disorders of the central nervous system have become one of the most common and most debilitating diseases currently afflicting mankind. Specific disorders such as depression and schizophrenia are now known to be common afflictions, and are routinely diagnosed. These diseases result in significant losses of an individual's ability to work and to carry out normal daily activities, and in many cases require long term hospitalization or institutionalization. Only recently have new treatments, such as the selective serotonin re-uptake inhibitors for example, become available and are effective for many people. Unfortunately, such agents are not effective for all cases of depression, and indeed can lead to significant adverse reactions in some patients.

Other CNS disorders, such as chronic pain and seizure disorders, are only marginally treatable, and such treatments often are associated with unacceptably high health risks, for instance long term use of narcotic analgesics to treat chronic pain generally results in addiction to the drug being employed, the results of which can be devastating to the patient.

Accordingly, the need continues for new medicines that will effectively treat CNS disorders without imposing unacceptable liability and risk issues. I have now discovered a series of aromatic amides which can be utilized to treat these CNS disorders, and which have a very good risk-to-benefit ratio. The invention compounds are alkyl amides having an aromatic group attached to the amide nitrogen atom.

Several N-aryl alkylamides are known in the prior art. For example, Ronsisvalle *et al.* described a series of analgesic N-thienyl acetamides in Eur. J. Med. Chem. 3: 553-559, 1998.

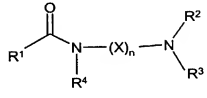
US Patent No. 4,203,988 discloses certain N-pyridyl amide derivatives as inhibitors of gastric secretion, while US No. 3,163,645 discloses N-pyridyl amides as analgesics. US No. 5,372,931 discloses N-alkoxyphenyl and N-alkoxynaphtyl amides as useful in certain analytical and diagnostic methods.

Elslager *et al.*, in J. Med. Chem. **9**: 378-91, 1966, describe certain N-naphthyl amides as useful as intermediates in the synthesis of arylazo substituted naphthyl alkylenediamines. Similarly, Elslarger *et al.*, described certain N-quinolyl amides in J. Med. Chem. **12**: 600-7, 1966.

The compounds provided by this invention are characterized as novel N-aryl amides having good CNS activities, and are thus useful for treating depression, anxiety, pain, schizophrenia, and seizure disorders such as epilepsy.

SUMMARY OF THE INVENTION

This invention provides N-aryl alkylamides defined by Formula I



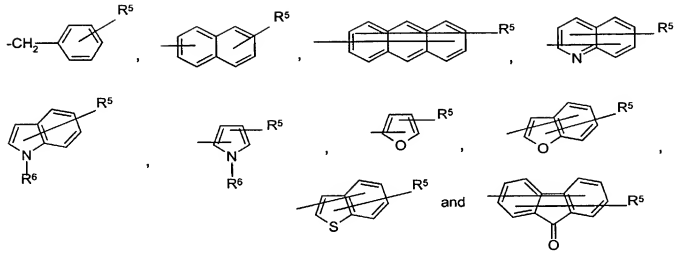
(I)

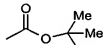
wherein :

R^1 is hydrogen, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

R^2 and R^3 independently are hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl or benzyl, or taken together with the nitrogen to which they are attached complete a ring having from 4 to 7 ring atoms, one optionally being oxygen; X is $(CH_2)_n$, CHMe-$(CH_2)_{n-1}$ or $(CH_2)_{n-1}$-CHMe, n is 1, 2 or 3;

R^4 is an aromatic or heteroaromatic group selected from



wherein R^5 is hydrogen, halogen, C_1-C_4 alkyl, nitro, N_3 or CF_3 and R^6 is hydrogen, C_{1-4} alkyl, -(C=O)Me, -(C=O)NH_2,  or  , and the pharmaceutically acceptable salts thereof.

Preferred invention compounds have Formula I wherein R^1, R^2 and R^3 independently are C_1-C_4 alkyl, and R^4 is naphthyl, substituted naphthyl, fluorene or substituted fluorene. Also preferred are the compounds of Formula I wherein n is 2 or 3.

Another embodiment of this invention is a pharmaceutical formulation comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier, diluent or carrier therefor.

The compounds of the instant invention are useful for the treatment of CNS disorders including neurodegenerative disorders, pain, depression, convulsions, anxiety, schizophrenia and seizures.

Neurodegenerative disorders include, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia. A patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

Pain refers to acute as well as chronic pain.

Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain and allodynia.

Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive.

Still other pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache.

Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, IBS and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

The compounds of the instant invention are also expected to be useful in the treatment of anxiety, panic, schizophrenia and seizures as demonstrated by means of standard pharmacological procedures.

The invention also provides a method for treating CNS disorders in mammals, comprising administering a CNS effective amount of a compound of Formula I to a mammal in need of treatment.

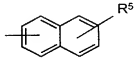
DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C_1-C_4 alkyl" means straight and branched carbon chains having from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, *n*-butyl, *sec*-butyl and *tert*-butyl.

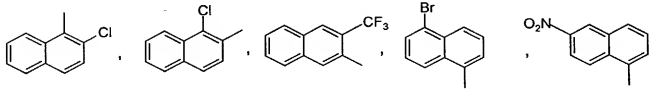
"C_2-C_4 alkenyl" means ethylene, 2-propylene and 2- or 3-butylene.

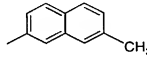
"Halo" means fluoro, chloro, bromo and iodo.

"Substituted aryl" and "substituted heteroaryl" means any of the cyclic ring systems described above having R^5 other than hydrogen, for example where R^5 is halo, C_1-C_4 alkyl, nitro or CF_3. Typical substituted aryl and substituted heteroaryl groups thus include 3-chloronaphthyl, 4-nitronaphthyl, 4-nitrobenzofuranyl, 3-methylbenzothienyl, and 1-methyl-3-trifluoromethyl indole. These are compounds of Formula I wherein R^4 is a cyclic, bicyclic or tricyclic aromatic or heteroaromatic group bearing a substituent defined as R^5, where R^5 is other than hydrogen. The group

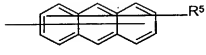


is a naphthyl ring which can be attached to the amide nitrogen (of Formula I) at any ring position. This ring can be substituted at any available ring position by the group R^5. Specific examples include :



and 

Specific examples of the group:



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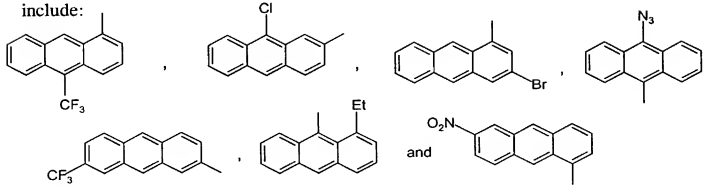

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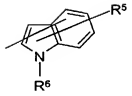

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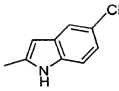
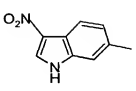
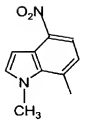
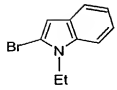
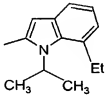
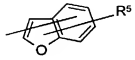





and



Specific examples of the group:



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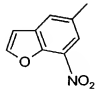
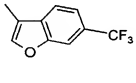
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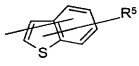

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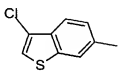
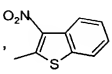
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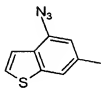

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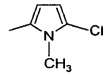
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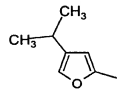
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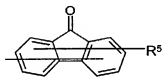

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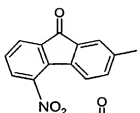
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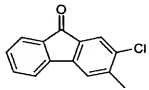
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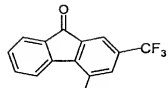
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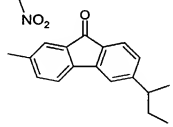
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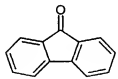
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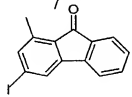

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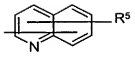

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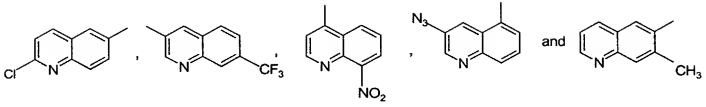

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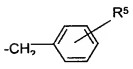

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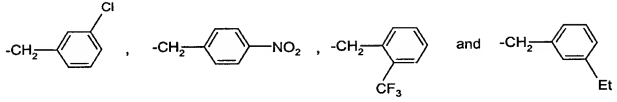
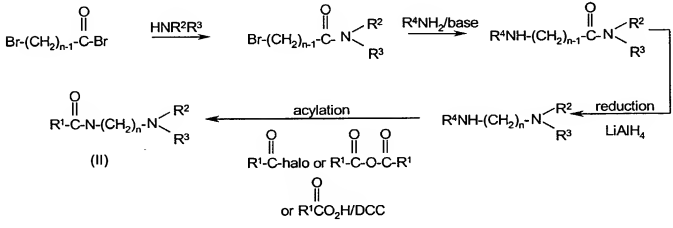


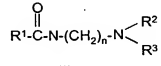
The compounds of this invention are amines and as such they readily form pharmaceutically acceptable salts by reaction with common inorganic and organic acids. Typical acids commonly used to form salts include hydrochloric, nitric, phosphoric , and sulfuric acid, as well as acetic, citric, malonic, tartaric, succinic, salicylic, methanesulfonic, oxalic and benzoic acid. Any common inorganic or organic acid can be utilized to form the pharmaceutically acceptable salts of this invention, and the specific acid to be utilized is well within the skill of the art.

The compounds provided by this invention can be prepared by any of several methods well known to those of ordinary skill in the art of organic chemistry. In a typical synthesis, an N-aryl alkyl diamine is acylated, for example by reaction with an aryl halide, or by

coupling an aryl-acid to the amide in the presence of a common peptide coupling reagent such as DCC (dicyclohexylcarbodiimide). Such synthesis can be illustrated by Scheme 1, in which an alkyl diamine is first prepared by reacting a halo substituted acyl halide with an amine HNR^2R^3, to give the corresponding halo substituted amide, reacting the halo substituted amide with an aryl amine $ArNH_2$ to give an arylaminoamide, reducing the amide carbonyl to give the corresponding arylamino alkylamine, and then acylating the arylamino nitrogen atom to give a compound of Formula II. The synthetic sequence is illustrated in scheme 1:



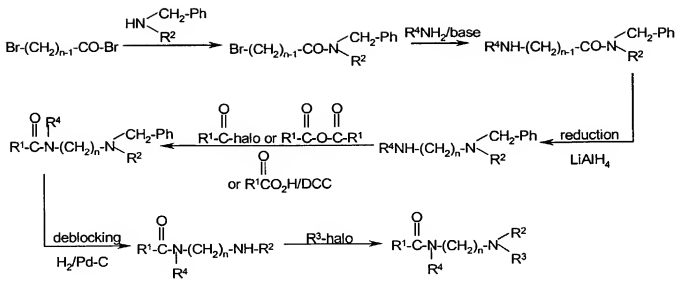
An alternative method for preparing the invention compounds comprises alkylating a terminal primary or secondary amine of the formula



(II)

where one or both of R^2 and R^3 are hydrogen, by reaction with an alkylating agent such as an alkyl halide. The reaction is depicted by scheme 2, which illustrates the synthesis of the primary or secondary amine according to the general scheme shown above, followed by a reaction with a common alkylating agent.

Scheme 2



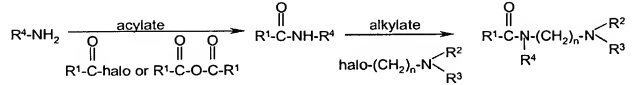
In the above scheme, the halo substituted acid halide is reacted with an amine bearing a group that is easily removed, such as benzyl. This is a normal acylation reaction that is typically carried out in a solvent such as dichloromethane or toluene, and generally is complete within 30 min to 1 h when carried out at a temperature of about 30°C to about 60 °C. The resulting amide is readily isolated by removing the solvent, and is subsequently reacted with an amine R^4NH_2 in the presence of a base such as sodium carbonate or triethylamine, and typically in a solvent such as N,N-dimethylformamide or diethyl ether. The resulting amino substituted amide is readily isolated by removing the solvent, and further purification generally is not required. The amino substituted amide is readily reduced by reaction with a reducing agent such as lithium aluminium hydride or sodium borohybride, thus affording an alkylene diamine. The alkylene diamine is coupled to an acyl group, for example by common acylation with an acid anhydride or acid halide (e.g. R^1-C(=O)-O-C(=O)-R^1 or R^1-C(=O)-halo, or by reacting the free acid R^1COOH with the amine using a coupling reagent such as dicyclohexylcarbodiimide (DCC).

The corresponding amide is next converted to a primary or secondary amine, for instance by removing a group such as benzyl by normal catalytic hydrogenation. The resulting amine is reacted with a common alkylating agent such as an alkyl halide (R^3-halo) and the

resulting product of Formula I is isolated by removing any reaction solvent and excess alkylating agent. The invention compound can be further purified if desired by routine methods such as crystallization, for example from solvents such as methanol, diethylether, ethyl acetate and the like, or chromatography over solid supports such as silica gel.

Still another way to prepare the invention compounds is to start with an aryl amine (R^4NH_2), acylate it with and acyl halide or anhydride to form an amide, and then alkylate the amide with an amino substituted alkyl halide. This process is depicted in Scheme 3 below :

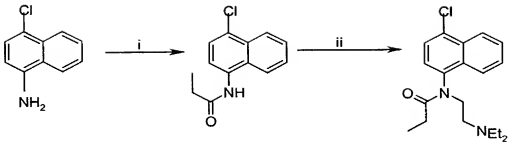
Scheme 3



These reactions are carried out under normal organic synthetic conditions. For example, an aryl amine such as 3-naphthylamine can be reacted with acetyl chloride in a solvent such as toluene. A base such as triethylamine can be utilized as an acid scavenger if desired. The reaction is substantially complete within 1 to 2 h when carried out at about 30 to 60 °C, and the product amide is readily isolated by removing the reaction solvent. The amine is then alkylated by reaction with an amino substituted amino alkyl halide to produce the invention compound of Formula I.

The synthesis of specific invention compounds is further illustrated by the following detailed example. The examples are representative only, and are not intended to limit the invention in any respect.

EXAMPLE 1



Reagents : (i) propionyl chloride, Et_3N ; (ii) NaH, $Et_2NCH_2CH_2Cl.HCl$

N-Propionyl 1-amino-4-chloronaphthalene.

To a stirred solution of 1-amino-4-chloronaphthalene (0.70 g, 3.9 mmol) in dichloromethane (50 ml) was added triethylamine (1.0 ml, 7 mmol), followed by propionyl chloride (0.5 ml, 5.8 mmol). After 20 min the mixture was diluted with ethyl acetate (150 ml) and washed with 2N HCl (100 ml) followed by saturated sodium carbonate (100 ml). The organic phase was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was triturated with a mixture of ethyl acetate and heptane, 130 ml, 3:10) to give 0.62 g (67 %) of the desired compound as a white solid.

^1H NMR 400 MHz ($CDCl_3$) : ™ 1.33 (3H, t, J = 6Hz) ; 2.56 (2H, q, J = 6Hz) ; 7.47 (1H, br s) ; 7.52-7.70, 4H, m) ; 7.84 (1H, m) ; 8.32 (1H, m).

MS ES^+: m/z 236 ($[MH]^+$, 16%), 234 ($[MH]^+$, 48%).

IR (thin film) λ_{max} (cm^{-1}) : 1652, 2922, 3300.

N-Propionyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene.

To a stirred solution of N-propionyl 1-amino-4-chloronaphthalene (400 mg, 1.7 mmol) in dry dimethylformamide (40 ml) was added sodium hydride (60% dispersion in oil, 0.2 g, 5 mmol). After 20 min, 2-diethylaminoethylchloride hydrochloride (0.4 g, 2.8 mmol) was added and the mixture stirred for a further 2 h. Water (200 ml) was added and the mixture extracted with ethyl acetate (2 x 100 ml). The organic extracts were combined, dried

($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by reverse phase chromatography (methanol:water 7:3) to give 0.27 g (47%) of the desired product as a colorless oil.

^{1}H NMR 400 MHz ($CDCl_3$): ™ 0.97 (9H, m); 1.80 (1H, m); 2.01 (1H, m); 2.50 (4H, m); 2.69 (2H, t, J = 7Hz); 3.34 (1H, m); 4.33 (1H, m); 7.36 (1H, d, J = 8 Hz); 7.55-7.70 (3H, m); 7.84 (1H, m); 8.34 (1H, d, J = 8 Hz).

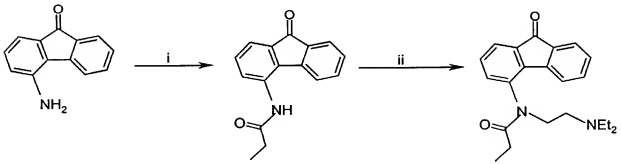
MS CI: m/z 233 ($[MH]^+$, 100 %).

IR (thin film) λ_{max} (cm^{-1}): 1667, 2970.

Microanalysis for $C_{19}H_{25}N_2OCl$

Calculated	C	68.56%	H	7.57%	N	8.42%
Found		68.29%		7.78%		8.20%

EXAMPLE 2



Reagents : (i) propionyl chloride, Et_3N ; (ii) NaH, $Et_2NCH_2CH_2Cl.HCl$

N-Propionyl 4-amino-9-fluorenone.

To a stirred solution of 4-amino-9-fluorenone (0.20 g, 1.0 mmol) in dichloromethane (40 ml) was added triethylamine (0.5 ml, 3.5 mmol), followed by propionyl chloride (0.5 ml, 5.8 mmol). After 20 min the mixture was diluted with ethyl acetate (150 ml) and washed

with 2N HCl (100 ml) followed by saturated sodium carbonate (100 ml). The organic phase was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, heptane:ethyl acetate 7:3) to give 164 mg (63%) of the desired material as a yellow oil.

^{1}H NMR 400 MHz ($CDCl_3$): ™ 1.36 (3H, br t); 2.56 (2H, br q); 7.18-7.38 (4H, m); 7.41-7.60, (2H, m); 7.71 (1H, d, J = 8 Hz); 7.83 (1H, br s).

IR (thin film) ν_{max} (cm^{-1}): 1659, 1716, 3258.

N-Propionyl, N-(2-diethylaminoethyl)-4-amino-9-fluorenone.

N-propionyl 4-amino-9-fluorenone (158 mg, 0.6 mmol) was dissolved in dry dimethylformamide (40 ml) and sodium hydride (60% dispersion in oil, 80 mg, 1.2 mmol). After 20 min, 2-diethylaminoethylchloride hydrochloride (250 mg, 1.4 mmol) was added and the mixture was heated to 80°C. After 10 min the mixture was cooled to room temperature and diluted with water (20 ml). The mixture was diluted with saturated sodium carbonate (150 ml) and the mixture extracted with ethyl acetate (2 x 70 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, dichloromethane:diethyl ether 9:1, and then 1:4) to give 0.16 g (73%) of the desired product as a colorless oil.

^{1}H NMR 400 MHz ($CDCl_3$): ™ 0.95 (6H, t, J = 7 Hz); 1.05 (3H, t, J = 7 Hz); 2.08 (2H, m); 2.50 (4H, m); 2.69 (2H, m); 3.34 (1H, m); 4.34 (1H, m); 7.30-7.75 (7H, m).

MS CI : m/z 351 ($[MH]^+$, 100 %).

IR (thin film) ν_{max} (cm^{-1}): 1652, 1716, 2970.

Microanalysis for $C_{22}H_{26}N_2O_2$

Calculated	C	75.40%	H	7.48%	N	7.99%
Found		75.55%		7.57%		7.94%

EXAMPLES 3-15

By following the general procedure of Examples 1 and 2, several additional compounds of Formula I were prepared and are described in Table I below.

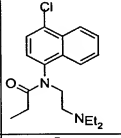
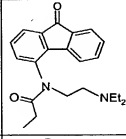
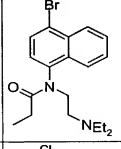
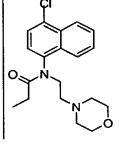
The compounds of Formula I have been evaluated in standard in vivo and in vitro assays routinely used to measure the ability of test compounds to interact with the central nervous system of animals, thereby establishing their utility for treating CNS disorders such as pain, depression, anxiety and schizophrenia. In a typical assay, compounds are evaluated for their ability to bind to the $\alpha_2\delta$ submit of the calcium channel found in animal brain tissue. Significant binding to this receptor indicates a compound's analgesic potential.

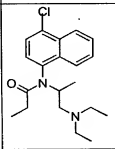
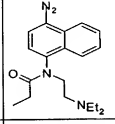
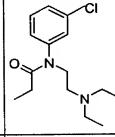
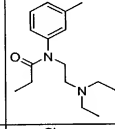
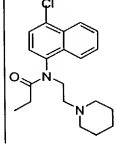
In another test, compounds were evaluated for their ability to reduce the hyperalgesia effects of carrageenin in the following assay: nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesimeter (Randall L.O. and Selitto J.J., A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn. 4: 409-419, 1957). Male Sprague-Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat Nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, 2 to 3 baseline measurements were taken before animals were administered 100 µl of 2 % aqueous carrageenin by intraplantar injection into the right hind paw.

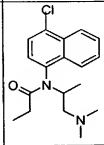
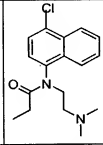
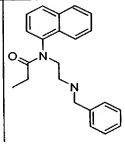
Nociceptive thresholds were taken again 3 h after carrageenin injection to establish that animals were exhibiting hyperalgesia. Animals were orally dosed with a compound of Formula I (by gavage) at 3.5 h after carrageenin injections and nociceptive thresholds were examined at 1 and at 2 h post-carrageenin.

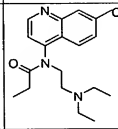
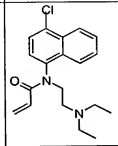
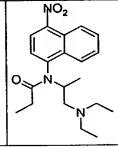
Table 1 presents the biological activity of representative invention compounds when evaluated in the above tests, and in the in vitro $\alpha_2\delta$ binding assay as described by Gee et al. in J. Biol. Chem., 1996; 271: 5776-5879, incorporated herein by reference.

Table 1

Compound	Structure	IC_{50}(μM) at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat	
			%MPE* 1h post dose @30mg/kg p.o.	%MPE* 2h post dose @30mg/kg p.o.
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene **(Example 1)**		0.170	51.5	22.2
N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone **(Example 2)**		0.058	1.1	6.4
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-bromonaphthalene **(Example 3)**		0.065	-2.6	7.7
N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene **(Example 4)**		>10	44.8	30.7

Compound	Structure	IC_{50}(μM) at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat: %MPE* 1h post dose @30mg/kg p.o.	Carrageenin induced thermal hyperalgesia in the rat: %MPE* 2h post dose @30mg/kg p.o.
N-Propionyl, N-(2-(3-diethylamino-propyl))-1-amino-4-chloronaphthalene **(Example 5)**		5.03	23.3	27.5
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene **(Example 6)**		0.885	N/A	N/A
N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzylamine **(Example 7)**		1.7	N/A	N/A
N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine **(Example 8)**		4.81	N/A	N/A
N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene **(Example 9)**		> 10	N/A	N/A

			Carrageenin induced thermal hyperalgesia in the rat	
Compound	**Structure**	**IC_{50}(μM) at $\alpha_2\delta$ binding site**	**%MPE* 1h post dose @30mg/kg p.o.**	**%MPE* 2h post dose @30mg/kg p.o.**
N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene **(Example 10)**		2.336	N/A	N/A
N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene **(Example 11)**		5.34	N/A	N/A
N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene **(Example 12)**		> 10	29.68	3.13

Compound	Structure	$IC_{50}(\mu M)$ at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat: %MPE* 1h post dose @30mg/kg p.o.	Carrageenin induced thermal hyperalgesia in the rat: %MPE* 2h post dose @30mg/kg p.o.
N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide **(Example 13)**		5.47	8.6	1.2
N-Acryloyl,N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene **(Example 14)**		0.177	15.1	0.9
N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene **(Example 15)**		0.800	-5.7	2.0

*MPE: maximum possible effect – set as baseline value prior to treatment with carrageenin

As noted above, the invention compounds of Formula I are typically utilized in the form of pharmaceutical compositions for human therapy of CNS disorders. The compounds can be formulated with any excipient, diluent or carrier commonly utilized in the pharmaceutical art. Such common excipients include potato starch, corn starch, talc, sucrose, lactose, cellulose; flavoring agents such as peppermint, orange flavor and the like. Binders and lubricants such as magnesium stearate, colloidal silicon dioxide and gum tragacanth can be utilized for convenient oral or parenteral administration, for example as tablets, capsules, aqueous solutions, elixirs, syrups, and controlled release patches, pellets and suppositories, as well as solutions for IV, SC and IM injection. The formulations will typically contain from about 5 % to about 95 % of active compound of Formula I (w/w).

The preparations will be administered such that the active ingredient is presented at a dose which is effective to treat a CNS disorder. Such dose will generally be from about 0.1 to about 2000 mg/kg of body weight, typically about 1 mg to about 100 mg/kg. The formulations can be administered from 1 to about 4 times a day, or as otherwise dictated by the particular patient and condition being treated, and the attending medical practitioner.

The compounds of Formula I can additionally be utilized in combination with other active ingredients, for example selective serotonin re-uptake inhibitors such as fluoxetine hydrochloride, and any of the tricyclic antidepressants such as benzazepines and the like.

The following examples further illustrate specific formulations provided by this invention.

EXAMPLE 16

Tablets

N-Butyryl, N-(3-dimethylamino-propyl)-5-amino-indole	200 mg
Potato starch	50 mg
Magnesium stearate	25 mg
Talc	25 mg

The above ingredients are blended to uniformity and then pressed into a tablet. Such tablets are administered from 1 to 4 times a day to an adult human suffering from depression and in need of treatment.

EXAMPLE 17

Capsules

N-pivaloyl 1-amino-2-trifluoromethyl-naphthalene	300 mg
Corn starch	50 mg
Dextrose	50 mg
Magnesium oxide	1 mg

The above ingredients are blended to uniformity and filled into an empty telescoping gelatin capsule. Such capsules are administrated from 1 to 4 times a day to an adult human suffering from schizophrenia and in need of treatment.

EXAMPLE 18

Parenteral solution

N-propionyl,N-(2-diethylaminoethyl)(1-amino-4-bromonaphthalene), hydrochloride salt	500 mg
isotonic saline	qs 1000 ml

The invention compound is dissolved in 1000 ml of isotonic saline and filled into a sterile plastic bottle equipped with a drip tube. The solution is administered IV to a human suffering from chronic pain resulting from colon carcinoma.

EXAMPLE 19

Transdermal skin patch

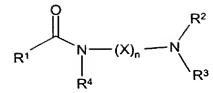
N-acetyl, N-(3-(N-ethyl-N-isobutyl)aminopropyl-3-amino-6-bromofluorene	450 mg
propylene glycol	10 mg
elastomer	5 mg
methyl cellulose	50 mg
sodium carboxymethyl cellulose	25 mg

The above ingredients are blended and spread onto an elastic tape. The tape is applied to the skin surface of a mammal to prevent and treat migraine pain.

The compounds of Formula I are useful for treating all conditions resulting from disorders within the central nervous system in animals, including humans. Commonly treated conditions include pain, depression, anxiety and schizophrenia. Other conditions that can be treated according to this invention include seizure disorders, i.e. epilepsy, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheirmer's disease, migraine, cerebral ischemia, and compulsive disorders such as narcotic addiction, alcoholism, smoking addiction, appetite disorders such as bulimia and obesity, sexual performance, and sleeping disorders.

What is claimed is:

1. A compound of formula I



wherein :

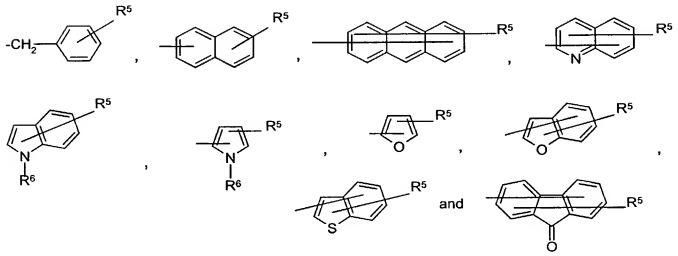
R^1 is hydrogen, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

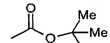
R^2 and R^3 independently are hydrogen, C_1-C_4 alkyl, phenyl or benzyl, or taken together with the nitrogen to which they are attached complete a ring having from 4 to 7 ring atoms, one optionally being oxygen;

X is $(CH_2)_n$, CHMe-$(CH_2)_{n-1}$ or $(CH_2)_{n-1}$-CHMe,

n is 1, 2 or 3;

R^4 is an aromatic or heteroaromatic group selected from



wherein R^5 is hydrogen, halogen, C_1-C_4 alkyl, nitro, N_3 or CF_3 and R^6 is hydrogen, C_{1-4} alkyl, -(C=O)Me, -(C=O)NH_2,  or  ;

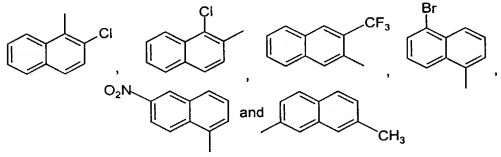
and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R^1 is C_1-C_4 alkyl.

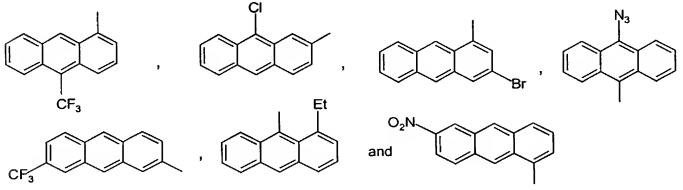
3. A compound according to Claim 2 wherein R^2 and R^3 independently are C_1-C_4 alkyl.

4. A compound according to Claim 3 wherein n is 2 or 3.

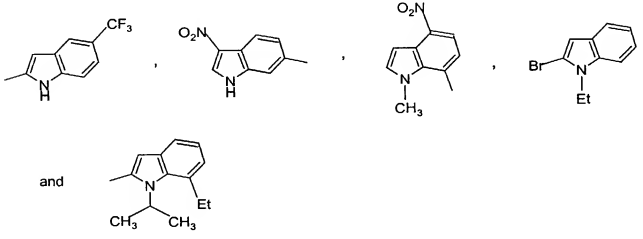
5. A compound according to Claim 4 wherein R^4 is selected from



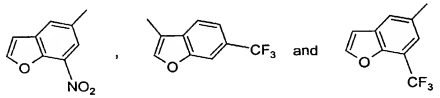
6. A compound according to Claim 4 wherein R^4 is selected from



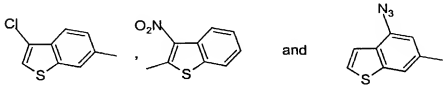
7. A compound according to Claim 4 wherein R^4 is selected from



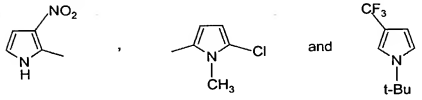
8. A compound according to Claim 4 wherein R^4 is selected from



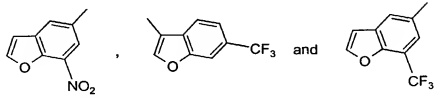
9. A compound according to Claim 4 wherein R^4 is selected from



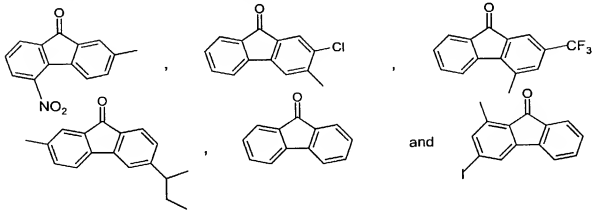
10. A compound according to Claim 4 wherein R^4 is selected from



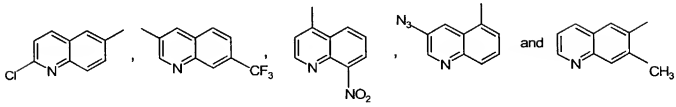
11. A compound according to Claim 4 wherein R^4 is selected from



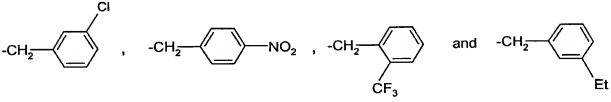
12. A compound according to Claim 4 wherein R^4 is selected from



13. A compound according to Claim 4 wherein R^4 is selected from



14. A compound according to Claim 4 wherein R^4 is selected from



15. A compound according to any one of Claims 5 to 14 which is selected from

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone

N-Propionyl, N-(2-Diethylaminoethyl)- 1-amino-4-bromonaphthalene

N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2- (3-diethylamino-propyl))-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzyl-amine

N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine

N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene

N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide

N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene, and

N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

16. N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene.

17. N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone.

18. N-Propionyl, N-(2-Diethylaminoethyl)- 1-amino-4-bromonaphthalene.

19. N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene.

20. N-Propionyl, N-(2- (3-diethylamino-propyl))-1-amino-4-chloronaphthalene.

21. N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene.

22. N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene.

23. N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

24. A compound according to any one of Claims 1 to 23 which is a pharmaceutically acceptable salt.

25. A pharmaceutical formulation comprising a compound of any one of Claims 1 to 24 together with a pharmaceutically acceptable diluent, carrier or excipient therefor.

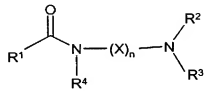
26. A method for treating a CNS disorder in a mammal in need of treatment comprising administering a CNS effective amount of a compound of any one of Claims 1 to 24.

27. A method according to claim 26 wherein the CNS disorder is selected from pain, depression, anxiety, or schizophrenia.

28. A method according to Claim 26 wherein the CNS disorder is selected from Huntington's disease, Alzheimer's disease or amyotrophic lateral sclerosis.

ABSTRACT OF THE DISCLOSURE

Aromatic and heteroaromatic amides of the formula



where R^1, R^2 and R^3 can be alkyl, X is alkylene, and R^4 is an unsubstituted or substituted aromatic or heteroaromatic group such as naphthyl or fluorenyl,
are CNS agents useful for treating pain, depression, anxiety, seizures, and schizophrenia.

10019993 060502

06 MAY 2002

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
225/50755

10/019993

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
NETWORKED VEHICLE COMMUNICATIONS SYSTEM COMPRISING A FRONT-END UNIT, A TERMINAL THAT CAN BE OPERATED BY A USER, AND A CORRESPONDING APPLICATION

the specification of which (check only one item below):

[ ] is attached hereto.

[X] was filed as United States application
Serial No. 10/019,993 on December 26, 2001,
And was amended
on _____ (if applicable).

[ ] was filed as PCT international application
Number PCT/EP00/04336 on May 13, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations. §1.56(a).

I hereby claim foreign priority benefits under Title 35, United State Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
Germany	199 29 331.7	June 26, 1999	[X] Yes [ ] No
			[ ] Yes [ ] No
			[ ] Yes [ ] No
			[ ] Yes [ ] No
			[ ] Yes [ ] No

Combined Declaration For Patent Application and Power of Attorney (Continued) (includes Reference to PCT international Applications	ATTORNEY'S DOCKET NUMBER 225/50755

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national of PCT international filing date of this application

PRIOR U S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U S FOR BENEFIT UNDER 35 U.S.C. 120

U.S. APPLICATIONS		STATUS *(Check one)*		
U.S. APPLICATION NUMBER	U S FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.

PCT APPLICATION NO	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (IF ANY)			
EP00/04336	May 13, 2000				

POWER OF ATTORNEY As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (List name and registration number)

Herbert I Cantor, Reg. No. 24,392, James F. McKeown, Reg. No. 25,406; Donald D Evenson, Reg. No. 26,160, Joseph D. Evans, Reg No. 26,269; Gary R. Edwards, Reg. No. 31,824, and Jeffrey D. Sanok, Reg No 32,169

Send Correspondence to:	Direct Telephone Calls to. *(name and telephone number)*
Crowell & Moring, L.L.P. P.O. Box 14300 Washington, D C. 20044-4300	(202) 624-2500

201	FULL NAME OF INVENTOR	FAMILY NAME GÖBEL	FIRST GIVEN NAME Fridjof	SECOND GIVEN NAME
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	POST OFFICE ADDRESS	POST OFFICE ADDRESS Christofstrasse 4	CITY D-74354 Besigheim	STATE & ZIP CODE/COUNTRY Germany
202	FULL NAME OF INVENTOR	FAMILY NAME HAHN	FIRST GIVEN NAME Ralf	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY Main-Kastel	STATE OR FOREIGN COUNTRY Germany DEX	COUNTRY OF CITIZENSHIP Germany
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203	FULL NAME OF INVENTOR	FAMILY NAME HUDEL	FIRST GIVEN NAME Peter	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY Friedberg	STATE OR FOREIGN COUNTRY Germany DEX	COUNTRY OF CITIZENSHIP Germany
	POST OFFICE ADDRESS	POST OFFICE ADDRESS Schöne Aussicht 1	CITY D-61169 Friedberg	STATE & ZIP CODE/COUNTRY Germany

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE 28/02/2002	Date 20103102	DATE 21/03/2002

Combined Declaration For Patent Application and Power of Attorney (Continued) (includes Reference to PCT international Applications	ATTORNEY'S DOCKET NUMBER 225/50755

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1 56(a) which occurred between the filing date of the prior application(s) and the national of PCT international filing date of this application

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U S FOR BENEFIT UNDER 35 U S C 120

U S APPLICATIONS		STATUS *(Check one)*		
U.S. APPLICATION NUMBER	U S FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO	PCT FILING DATE	U S SERIAL NUMBERS ASSIGNED (IF ANY)			
PCT/EP00/04336	May 5, 2000				

POWER OF ATTORNEY. As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (List name and registration number)
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 204	SIGNATURE OF INVENTOR 205	SIGNATURE OF INVENTOR 206
DATE 21.03.02	DATE 20/03/2002	DATE 01/03/2002